Identifying Critical Windows of Exposure for Children's Health

Sherry G. Selevan,[1] Carole A. Kimmel,[1] and Pauline Mendola[2]

[1]National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC, USA; [2]National Health and Environmental Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, USA

Several authors have considered the importance of exposure timing and how this affects the outcomes observed, but no one has systematically compiled preconceptional, prenatal, and postnatal developmental exposures and subsequent outcomes. Efforts were undertaken to examine the information available and to evaluate implications for risk assessment for several areas: *a*) respiratory and immune systems, *b*) reproductive system, *c*) nervous system, *d*) cardiovascular system, endocrine system, and general growth, and *e*) cancer. Major conclusions from a workshop on "Critical Windows of Exposure for Children's Health" included *a*) broad windows of sensitivity can be identified for many systems but detailed information is limited; *b*) cross-species comparisons of dose to target tissue and better data on the exposure–dose–outcome continuum are needed; *c*) increased interaction among scientific disciplines can further understanding by using laboratory animal results in designing epidemiological studies and human data to suggest specific laboratory studies on mechanisms and agent–target interactions; and *d*) thus far, only limited attention has been given to peripubertal/adolescent exposures, adult consequences of developmental exposures, and genome–environment interactions. More specific information on developmental windows will improve risk assessment by identifying the most sensitive window(s) for evaluation of dose–response relationships and exposure, evaluation of biological plausibility of research findings in humans, and comparison of data across species. In public health and risk management, information on critical windows may help identify especially susceptible subgroups for specific interventions. *Key words*: children's health, developmental disorders, developmental toxicity, environmental health, risk assessment, teratogen, windows of vulnerability. — *Environ Health Perspect* 108(suppl 3):451–455 (2000).
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In a discussion of "highly susceptible period[s] of organogenesis," Wilson (*1*) described the importance of exposure timing within the developing organism, and how this ultimately affects the outcomes observed. His hypothetical example, limited to prenatal exposures, showed that the same exposure at different times would create a different spectrum of, in this case, malformations due to the timing of the development of different organ systems (Figure 1). Other authors have considered the importance of critical periods of vulnerability in the developing organism. For example, Rodier (*2*) presented a summary of experimental data on timing of neuron origin in the developing mouse brain (Figure 2). A time line for human development (Figure 3) identified highly sensitive windows for morphological abnormalities and compared them to less sensitive times that were more likely to be associated with physiological defects and minor morphological abnormalities (*3*). Later, an adaptation (Figure 4) of these efforts was made for commonly studied adverse outcomes for humans, broader than malformations and physiological defects, but still limited to preconceptional and prenatal exposures (*4*).

The U.S. Environmental Protection Agency (U.S. EPA) is concerned with the entire gamut of developmental exposures and outcomes, i.e., developmental toxicity. Developmental toxicity is defined as the occurrence of adverse effects on the developing organism that may result from exposure prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism. The major manifestations of developmental toxicity include death of the developing organism, structural abnormality, altered growth, and functional deficiency (*5*). Developmental exposures may result in health effects observed prenatally and at birth (such as spontaneous abortion, stillbirth, low birth weight, small for gestational age, infant mortality, and malformations) (*4,6–8*), in childhood (effects such as asthma, cancer, neurologic and behavioral effects) (*9–12*), and as adults and into old age (such as cancer, heart disease, and degenerative neurologic/behavioral disorders) (*13–16*).

Several authors have pointed out that little concrete information exists on critical windows for exposure during the postnatal period (*17,18*). However, a systematic examination has not yet been done of available data on critical windows of vulnerability to agents that may cause toxicity throughout prenatal and postnatal development. Most available data are focused on prenatal exposures (for example, maternal medications such as diethylstilbestrol or thalidomide, and parental alcohol, smoking, and occupational exposures) (*6–11,19–21*). Postnatal exposures have been examined for only a few agents (e.g., lead, pesticides, radiation) (*12–15*).

The effort reported in this monograph was undertaken to review the data available on the various types of preconceptional, prenatal, and postnatal developmental exposures and subsequent outcomes; to examine the state-of-the-science knowledge on critical windows of susceptibility; and finally, to evaluate their implications for risk assessment. To do this, experts were asked to prepare background papers summarizing current knowledge about critical windows for five topic areas: *a*) respiratory and immune systems (*22–24*); *b*) reproductive system (*25*); *c*) nervous system (*26*); and *d*) cardiovascular system, endocrine system, and general growth (*27–29*); and *e*) cancer (*30*). On 14–15 September 1999, a workshop, "Critical Windows of Exposure for Children's Health," was convened in Richmond, Virginia, with nearly 60 scientists from a variety of disciplines. This multidisciplinary group included expertise in clinical medicine, psychology, toxicology, epidemiology, and risk assessment. Participants were brought together to discuss current knowledge on critical windows of exposure, identify major issues for future

This article is based on a presentation at the Workshop to Identify Critical Windows of Exposure for Children's Health held 14–16 September 1999 in Richmond, Virginia, and the work group reports from that meeting.

Address correspondence to S.G. Selevan, U.S. EPA (8623D), Washington, DC 20460 USA. Telephone: (202) 564-3312. Fax: (202) 565-0078. E-mail: selevan.sherry@epa.gov

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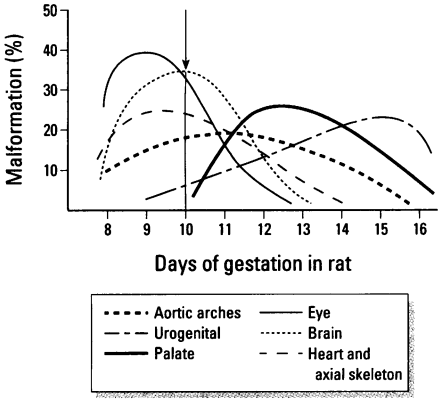

Figure 1. Hypothetical representation of how the syndrome of malformations produced by a given agent might be expected to change when treatment is given at different times. The percentage of animals affected as well as the incidence rank of the various types of malformations would be somewhat different from that shown for day 10 if treatment were given instead on day 12 or 14, for example. Reprinted with permission of University of Chicago Press (*1*).

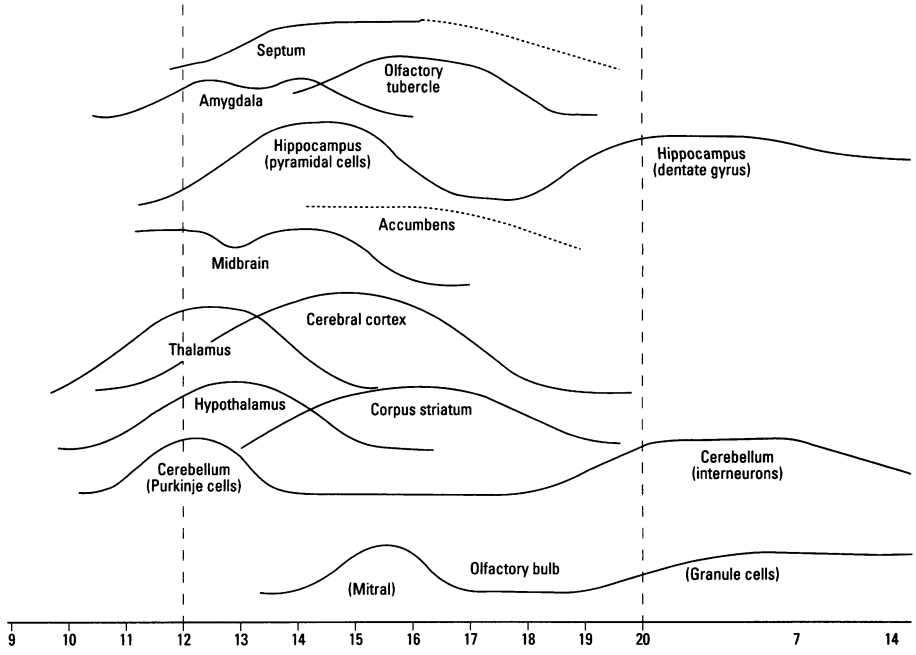

Figure 2. Times of neuron origin in the developing mouse brain. Times are based on autoradiographic studies of specific structures over time. Vertical lines at 12 days and 20 days represent the approximate end of critical period for gross defects and the time of birth, respectively. Reprinted with permission of John Wiley and Sons, Inc. (*2*).

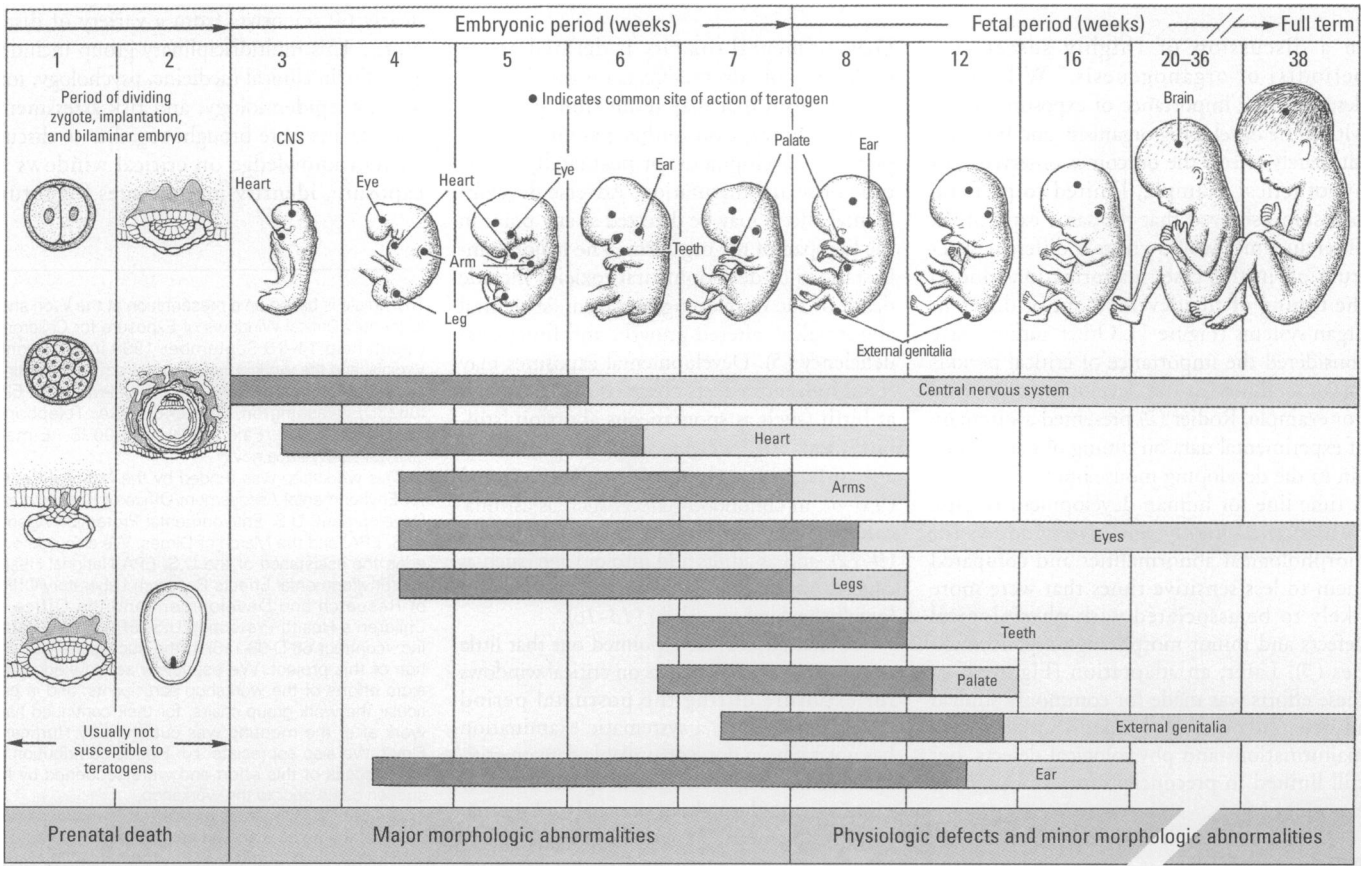

Figure 3. Schematic illustration of the sensitive or critical periods in human development. Dark gray denotes highly sensitive periods; light gray indicates stages that are less sensitive to teratogens. Reprinted with permission of W.B. Saunders Co. [(*3*); first published in 1973].

efforts, and determine how this information can ultimately be used for risk assessment and public health purposes.

Typically, studies of humans have used broad categories of exposure covering multiple windows. In laboratory animal studies, the early literature in experimental teratology was dominated by studies aimed at periods of known high sensitivity for producing certain types of malformations. More contemporary studies, in particular those done for regulatory testing purposes, often include extended periods to simulate long-term human exposure. For example, in the prenatal developmental toxicity study (*31*), dosing extends from implantation to term. Dosing in the two-generation reproduction study (*32*) is for several weeks preconception, then prenatally and postnatally for two generations. In the developmental neurotoxicity study (*33*), dosing usually begins at implantation and continues throughout prenatal development until midway through or to completion of the preweaning period to cover the major periods of nervous system development. In some cases, the developmental neurotoxicity study is combined with the two-generation study and animals are evaluated in the second generation. Occasionally, follow-up studies of short-term exposures are conducted to determine critical windows of sensitivity, but this is rare for environmental chemicals [for example, see Narotsky et al. (*34*)].

In humans, patterns of exposure are much more variable. Data on exposures to parents and children are frequently collected from "convenience" samples of individuals. Exposure data are collected at a time convenient for the researchers, often contemporaneous, but not necessarily at a biologically plausible time for the health effect. Alternatively, exposures during the relevant time frame must be recalled or reconstructed.

Exposure issues vary by life stage (preconception, prenatal, and postnatal). Important preconceptional exposures could be *a*) temporary, limited to those immediately preceding conception; *b*) at some earlier time (prior to conception), creating nonreversible conditions; or *c*) consist of an accumulation of an increased body burden accumulated over a long period of exposure. Prenatally, exposures often change throughout pregnancy due to choice or necessity. For example, women may choose to reduce or quit smoking, or may do so as a response to physical symptoms of pregnancy such as nausea. Layered on top of these variations, changes in internal dose may result from alterations in absorption, distribution, metabolism, and excretion during pregnancy (Table 1) (*35*). For example, with the increased pulmonary function, pregnant women exchange about 72% more air over 8 hr at rest (5,000 L in pregnant women vs 2,900 L in nonpregnant women) (*36*). Studies of prenatal exposures in humans frequently obtain one measure of exposure for the entire pregnancy because the investigators either assume that the exposure is consistent over time, or they lack the resources or sufficiently refined tools to obtain more detailed information. Additional issues are raised for studies which, by design, must estimate exposures retrospectively (e.g., case–control studies of birth defects). Since exposure data must be recalled, efforts can be made to reconstruct changes in exposure throughout gestation, but the data are subject to recall bias.

Finally, many studies of postnatal outcomes collect exposure data at the same time the child's health status is determined. Children's exposures change radically over time. At different developmental stages, the biology, behavior, and activities of children (Table 2) result in variable exposures among children and differences from adults in the same environment. For example, the surface area to body mass ratio in infants is approximately 2.7-fold greater than in adults, the respiratory minute ventilation rate is more than 65 times greater (*36*), and consumption of drinking water more than 2 times higher than adults per body weight (*37*). Even over the relatively short time span of childhood, these can vary widely. Thus, exposures identified concurrently with the observation of health status may not be similar to those occurring during the critical window(s) of exposure.

Because of a variety of factors, children have a greater potential for adverse health effects than adults. Children are still developing in many ways and may be more vulnerable. They may be less able to rid themselves of exposure due to immature mechanisms for detoxification; and because of differences in metabolism and behavior, they may reach higher levels of exposure within the same environment as adults. To better identify and understand the relationships among exposures and developmental outcomes, the first step is identification of key time periods for

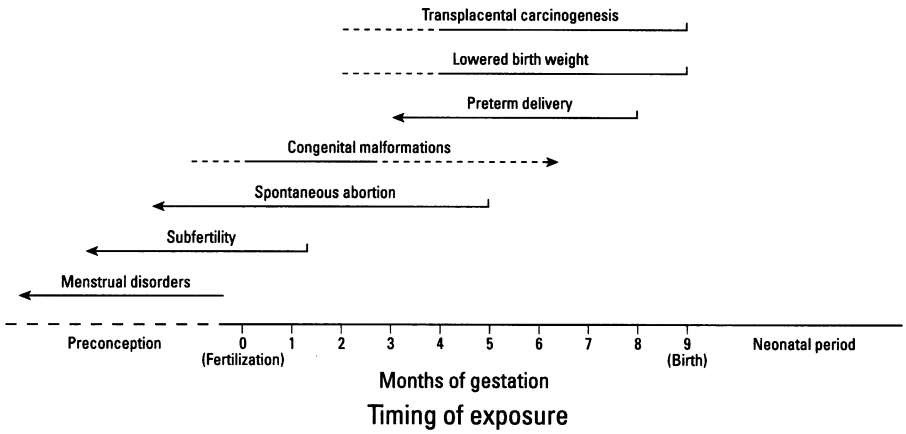

Figure 4. Reproductive outcomes associated with timing of maternal exposure. Solid lines indicate the most probable timing of exposure for a particular outcome; dotted lines indicate less probable but still possible timing of exposure. Arrows suggest that a defined cutoff point for exposure to a specific outcome is not known. Reprinted with permission of Lippincott, Williams and Wilkins (*4*).

Table 1. Physiologic and toxicokinetic changes during pregnancy.[a]

Parameter	Physiologic change	Toxicokinetic change
Absorption		
Gastric emptying time	Increased	Absorption increased
Intestinal motility	Decreased	Absorption increased
Pulmonary function	Increased	Pulmonary exposure increased
Cardiac output	Increased	Absorption increased
Blood flow to skin	Increased	Absorption increased
Dermal hydration	Increased	Absorption +/–
Metabolism		
Hepatic metabolism	+/–	Metabolism +/–
Extrahepatic metabolism	+/–	Metabolism +/–
Plasma proteins	Decreased	Metabolism +/–
Excretion		
Renal blood flow	Increased	Increased renal elimination
Glomerular filtration rate	Increased	Increased renal elimination
Pulmonary function	Increased	Increased pulmonary elimination
Plasma proteins	Decreased	Elimination +/–

[a]Modified from Silvaggio et al. (*35*).

Table 2. Differences in children and adults.

	Infants	Children	Teens	Adults	Reference
Surface area: body mass ratio (m^2/kg)	Newborn 0.067	Young child 0.047	Older child 0.033	Adult 0.025	(35)
Respiratory ventilation rates	Infant			Adult	(35)
Respiratory volume (mL/kg/breath)	10			10	
Alveolar surface area (m^2)	3			75	
Respiration rate (breaths/min)	40			15	
Respiratory minute Ventillation rate[a]	133			2	
Drinking water (tap)	< 1 year	1–10 years	11–19 years	20–64 years	(36)
Mean intake (mL/kg/day)	43.5	35.5	18.2	19.9	
Fruit consumption (g/kg/day)	< 1 year	3–5 years	12–19 years	40–69 years	(37)
Citrus fruits	1.9	2.6	1.1	0.9	
Other fruits (including apples)	12.9	5.8	1.1	1.3	
Apples	5.0	3.0	0.4	0.4	
Soil ingestion (mg/day)		500			(38)
Pica child		Child age 2.5 years		Adult	
Outdoor		50		20[b]	
Indoor		60		0.4	
Differences in GI absorption of lead	Age 0–2 years 42–53%	Age 2–6 years 30–40%	Age 6–7 years 18–24%	Adult 7–15%	(39)

[a]mL/kg body weight/m^2 lung surface area/min. [b]Gardening for adults.

specific outcomes. Data on these critical windows have not been previously compiled in a structured, systematic manner. The accompanying reports present the current understanding of critical windows, gaps in knowledge, the use of this information in the risk assessment process, and recommendations for future activities (*41–45*).

Some major themes were identified in these discussions. The first step in identifying critical windows involved tracking development of the systems examined. This allowed identification of times when the system is potentially most vulnerable to the action of toxic agents. Current information on the exact timing and sensitivity during these windows is limited, however. In those cases where information can be found, there may not be uniform sensitivity across the window, reinforcing the importance of detailed exposure assessment. For many developmental events, broad windows have been used, increasing the likelihood of misclassification of exposure.

Although most work groups used the approach described above, the Cancer Work Group was in a unique situation: They were addressing an outcome that could affect a wide variety of systems and might have many windows. The Cancer Work Group noted the importance of the development of a unifying model, ". . . a holistic pathogenetic model that encompasses childhood and adult cancers" (*45*), to move understanding forward.

The work group discussions identified similarities in reactions to agents with toxic potential for humans and laboratory animals. Some significant differences were also identified: *a*) Differences may affect delivery of an agent to the target, for example, placenta in humans versus yolk sac in rodents. *b*) Some developmental events occur postnatally in rodents but occur prenatally in humans; and the fact that "childhood" is very short in rodents. Because of the inherent differences, comparisons across species of the dose to the target tissue would be most informative. This highlights the need for better data on the exposure-dose–outcome continuum in both humans and laboratory animals.

The importance of increased interaction among different scientific disciplines was identified. Laboratory animal data could lead epidemiologists/clinicians to areas of potential concern in humans, and epidemiologic data could identify areas for laboratory investigators to develop mechanistic data and information on agent–target interactions. These could then feed into the development of more sensitive methods in both arenas, validation across species, and ultimate incorporation into future studies.

Other areas identified for future work include the following:

- While there has been increased interest in the examination of children's health, only limited attention has been given to adult consequences of developmental exposures. Not much is known about the potential cascade of events that might result in adverse outcomes. The association of developmental exposure with long-term health outcomes was discussed. For example, in the case where intrauterine growth retardation (IUGR) is associated with exposure, do those with exposure-related IUGR have the same later-life sequelae as individuals with IUGR due to nutritional or other developmental factors?
- Are those with certain genetic traits more likely to get cancer or other health conditions associated with developmental exposures? Limited data are available on gene–environment interactions, an area identified as important for future research.
- The peripubertal/adolescent period was identified as a life stage underrepresented in the current literature, despite the fact that many organ systems undergo significant development during this time.

What will these data mean for public health, risk assessment, and risk management? In hazard identification/dose–response assessment (*5*), information about developmental windows will aid in evaluation of the biological plausibility of research findings, comparison of data across species, and identification of the most sensitive window for the evaluation of dose–response relationships and exposure. In risk management, information on critical windows may help identify especially susceptible subgroups/ages for specific interventions.

A consistent picture appears across the topic areas: more information is needed on critical windows of development to improve assessment of potential environmental health risks.

Continuing dialogue among scientists from various disciplines can help in the effort to fill in the data gaps, improve measurement of exposures, and enhance the use of information on critical windows of exposure to improve estimates of risk for children's health.

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